

known sera in which the Wassermann was negative, the Herman-Perutz was positive.

The advantage of the reaction is its simplicity, but the disadvantages of the fewer positive reactions and lack of absolute specificity detract from its diagnostic value.

Variations in the Strength of the Wassermann Reactions in Untreated Syphilis. During the routine examination of sera for the Wassermann reaction at the Laboratory of the Army Medical School, Washington, D. C., C. F. Craig⁹ frequently observed cases in which the reaction varied from a strongly suspicious one to a plus-minus or negative one within intervals of one or two weeks, while in a few cases a positive reaction became negative within the same period of time, the patients meanwhile receiving no treatment. In all of these instances, subsequent tests of the blood serum resulted in a positive reaction, so that it was evident that these variations in the result must have depended on the reduction or absence of the body or bodies in the patient's serum which produce complement-fixation in the presence of an efficient antigen.

The fact that the blood-serum of an undoubted syphilitic patient during certain intervals may give a negative reaction, in the absence of specific treatment, and when previous and subsequent tests are positive, is of considerable importance in the interpretation of a negative result in any case suspected of the disease, and of significance in the study of the exact nature of the reaction. These anomalous results are not very numerous, but their occurrence, together with the criticisms of some writers who have had a similar experience, and who therefore appear to consider the test untrustworthy, renders an experimental study of the subject of value. Craig gives in detail the results obtained from the daily titration of the blood-serum in ten untreated cases of syphilis, the titration covering seven days in each instance.

While, *a priori*, there would appear to be no reason why the strength of the complement-fixation reaction in

(9) Jour. Amer. Med. Ass'n., April 18, 1914.

the blood-serum of untreated syphilitics should not vary markedly from day to day, nevertheless this phase of the subject appears to have received little attention, and we have grown to consider the strength of the reaction as an invariable quantity, the discordant results that have sometimes been obtained with the reaction either being imputed to the serologist, or considered as proof of the unreliability of the test. If this paper does nothing more, Craig says, it will demonstrate that marked daily variations do occur in the strength of the reaction, and that these must be most carefully considered in the interpretation of negative or anomalous results.

Ten patients suffering from undoubted syphilitic infection were selected for the experiments. Of these, two were in the primary stage of the disease, four in the secondary stage, and four in the latent stage of syphilis. The only patients who had received any treatment were those in the latent stage, and it had been over a year since any treatment had been administered to these cases. The two patients in the primary stage showed typical chancres, and later developed secondary lesions; the four in the secondary stage all showed typical eruptions or mucous lesions; while the four with latent infections were free from symptoms at the time of examination, but gave a typical history of infection, and had presented typical symptoms in the past. All of the patients with latent infections had been treated with salvarsan about one year before these tests were made.

Most of the men were prisoners in the U. S. Military Prison at Fort Leavenworth, and thus all chance of the strength of the reaction being influenced by the use of alcohol or by other irregularities was obviated, the men being under a rigid discipline and on a plain, wholesome diet. The serum was collected every morning in sterilized tubes and promptly tested.

Briefly summarized, the results in this investigation were as follows: In one case of primary syphilis, a plus or doubtful complement-fixation reaction was obtained on three of seven days, the reaction on four days being double-plus, or positive; in another case a plus or doubtful reaction was obtained on two of seven days. In one

case of secondary syphilis, a negative reaction was obtained on one day, a plus-minus on one day, a plus or doubtful reaction on three days, and a positive or double-plus reaction on two days; in another secondary case a plus or doubtful reaction was obtained on two of seven days. Of the latent cases, one gave a plus-minus reaction on two days and a plus reaction on four days of the week, a positive reaction being obtained only on one day; another gave a negative reaction on one day, a plus-minus on another, and a plus reaction on three days. The third latent case gave a plus or doubtful reaction on three of seven days, while the fourth case gave a double-plus reaction on all but one day of the seven.

The most important practical points brought out by these observations on the daily titration of the blood-serum of untreated syphilitics are that great variations may occur in the complement-binding power of the serum in patients uninfluenced by any kind of treatment; that a single negative or doubtful Wassermann reaction is of no value in excluding syphilis; and that the occurrence of these natural variations must be carefully considered in the diagnosis and the control of treatment of the disease.

There can be no question regarding the technique employed in the titration of these serums, as it was identical with that used in the routine Wassermann work, a technique that has been thoroughly controlled and checked by thousands of re-examinations of patients under treatment during four and a half years. Any interference with the reaction which might have been brought about by excesses of any kind is thought to have been impossible, as the patients, with two exceptions, were military prisoners, under strict discipline and on an ordinary diet. The influence of alcohol in rendering a positive Wassermann test negative, first called attention to by Nichols and Craig,¹ was one of the reasons why prisoners were selected for these tests.

The observations detailed in this contribution make still more evident the absolute worthlessness of a single negative reaction in eliminating syphilis in a suspected

(1) Jour. Amer. Med. Ass'n., August 5, 1911, p. 474.

person. In several of the cases under discussion the blood-serum, if tested only on certain days, would have given a negative, or practically negative, result, although serum from the same persons had previously given a positive result and again became positive within a day or two. If this be true of untreated individuals, some of them showing severe lesions of the disease, it will certainly be found true of a greater number of latent and treated infections, the very class of cases in which a negative Wassermann test is so often considered decisive as to the absence of the disease. The present propaganda for a eugenic law, in which a single, or even two, negative Wassermann reactions are to be relied on to exclude syphilis, does not take into consideration the very slight value of a negative result; and while such a law would be a step in the right direction, a dependence on such a standard alone will inevitably lead to a false sense of security and to the infection of innocent persons.

Interpretation of the Wassermann Reaction. Ravaut,⁴ in accord with many other writers, says that in a case presenting the clinical evidence of syphilis a positive reaction is definite proof of the presence of syphilis. On the contrary, there may be active luetic lesions with a negative reaction. Hence, a negative reaction will not eliminate syphilis.

In the treatment the physician should strive to obtain, and maintain, a negative reaction; one, or even several, negative reactions should not be justification for cessation of treatment. In old cases it is sometimes well-nigh impossible to obtain a negative reaction.

In a suspected case the Wassermann reaction should be looked upon merely as one of all the symptoms, which, when considered together, enable one to make a diagnosis. A persistently positive reaction in a patient presenting neither signs nor antecedents of syphilis should lead to a careful search for the evidence of the disease. In rare cases the reaction may be positive in the absence of syphilis. Therefore, a positive reaction alone is in-

(4) Annales Derm. Syph., May, 1914.

sufficient evidence on which to make a diagnosis of syphilis.

Cholesterolized and Non-Cholesterolized Artificial Antigens in the Wassermann Reaction. Since the introduction of cholesterolized antigen by Sachs from Ehrlich's laboratory, reports concerning its specificity have been conflicting, varying from the assertion that an artificial antigen had been found possessing the requirements of an ideal "standard antigen," to an assertion that it was unreliable, and hence a menace to the clinician.

In view of such diversity of opinion, it appeared desirable to C. C. W. Judd² to investigate its merits and to report the result of an investigation extending over a series of 400 reactions.

In a series of 379 sera and twenty-one spinal fluids, 269, or 71 per cent., of sera and fourteen, or 66.66 per cent., of spinal fluids gave identical results with standard cholesterolized antigen and Noguchi antigen.

In 110, or 29.05 per cent., of sera and seven, or 33.33 per cent., of spinal fluids, there was to a greater or less extent a lack of agreement between these two antigens. Of the 110 sera showing differences in complement-fixation, 105, or 95.4 per cent., showed greater complement-fixation with standard cholesterolized antigen than with Noguchi antigen, while five, or 4.6 per cent., showed greater inhibition of hemolysis with Noguchi antigen than with standard cholesterolized antigen. No spinal fluid exhibited the latter phenomenon.

Standard cholesterolized antigen does not yield an appreciable number of non-specific reactions; but, on the other hand, does detect many luetic cases which do not yield positive results with Noguchi antigen. Though amenable to the influence of treatment, it is less susceptible to extinction by therapeutic measures. It also possesses splendid keeping properties, is always available, and is easy of preparation. Judd considers it an ideal artificial antigen.

Sero-Enzyme Test for Syphilis. The infectious diseases offer a promising field for this line of investigation,

(2) Jour. Amer. Med. Ass'n., July 25, 1914.

since, in the course of such diseases, the causative organisms find their way into the circulation and there give rise to the protective enzymes capable of digesting them. We have in syphilis a disease simulating many other conditions in which cell-proliferation and destruction occur, so that the resorption of these broken-down foci by the blood will further stimulate the formation of enzymes against the protoplasm of the cells undergoing degeneration as the result of the presence of the *Spirocheta pallida* in the body.

Two hundred sera, obtained mostly from patients of an out-door clinic, form the basis for an investigation by F. W. Baeslack.³ The tissue employed was the "gummas" resulting from the inoculations of syphilitic tissue or blood into the testes of rabbits. These lesions become, in the course of a few transplantations from rabbit to rabbit, free from secondary infection. They are practically non-vascular and contain the *Spirocheta pallida* in large numbers. The author finds that the sero-enzyme test for syphilis, when carried out with syphilitic testicular tissue, is probably a specific reaction, since the somatic cells are highly specialized, presupposing a specific enzyme for their cleavage. In the use of the gumma produced in rabbits by inoculation, he makes use of a substratum which, when free from contamination, is superior to tissue prepared from the tissue of syphilitic patients, which of necessity is contaminated and is likely to give rise to positive reaction in other conditions.

The reaction is not applicable in cases in which cerebrospinal fluid is to be tested.

The reaction is more specific than the Wassermann reaction, for it gives a positive reaction with the serum of tabetics, while the Wassermann reaction in this condition is negative in about 40 per cent. of cases. He points out that nine cases of tuberculosis gave a positive Wassermann reaction, although no sign of syphilis could be found in any of these patients. The specificity of the test is further shown in eight cases giving a negative Wassermann reaction and a positive sero-enzyme test.

(3) Trans. Sec. Derm. A. M. A., 1914.

The technique of the reaction demands cleanliness and careful control of shells, tissue, serum, and the carrying out of the ninhydrin reaction. As one becomes acquainted with the test one's confidence in it increases.

The sero-enzyme test for syphilis represents, with the exceptions indicated, a true biologic test for this disease.

The Luetin Reaction in Syphilis. J. N. Muscel, C. A. Dersea and L. Friedmann⁴ state that the luetin test applied to sixty-two syphilitics and ninety-three patients with other diseases gave positive reactions in 89 per cent. of the cases of syphilis in the tertiary phase, in 20 per cent. of the cases of tabes, in 47 per cent. of the secondary phase cases, and in only 2 per cent. of the supposedly non-syphilis cases. Comparison with the Wassermann test showed the luetin test positive in two cases of secondary syphilis in which the Wassermann was negative, while in the tertiary phase there were twelve cases in which the Wassermann was negative and the luetin positive out of the total thirty-seven in this stage. These findings suggest, they say, that luetin is the more sensitive and reliable test in syphilis in the third stage or in latent form.

TREATMENT.

Salvarsan in Treatment of Syphilis. Owing to the number and conflicting character of the statements regarding the value of salvarsan in the treatment of syphilis, it is difficult to obtain a clear insight into what it really has accomplished and what we may reasonably hope to accomplish by its rational employment. For-dyce,⁵ in an admirable editorial, states his views regarding the use of this important drug.

A proper mental picture of syphilis can not be obtained from a one-sided view of the disease, such as a study of the primary lesion and the secondary manifestations on the skin or mucosa, but from the viewpoint of a general infection. It is worth while to study the variations presented by the primary focus of infec-

(4) Münch. med. Wochenschr., June 9, 1914.

(5) Jour. Cut. Dis., January, 1914.

tion and the multiform character of the eruption, but we must go beyond this and think of the disease as a general one which produces its most serious results on the nervous system, the vascular apparatus, and the eye. It must furthermore be borne in mind that syphilis in its early stages invades all the tissues and may cause gross lesions with objective manifestations or may maintain a latency lasting for many years. The most important clinical fact which has been confirmed by the exact diagnostic methods of the past few years is that the nervous system is infected early, but that here, as in other parts of the body, the disease may also remain latent for years, before producing more than occasional transient symptoms. The control of the treatment of the disease in the first year by the Wassermann reaction and lumbar puncture, if systematically pursued, will probably do much in preventing the development of this latent or active infection of the nervous system. We must rid ourselves of the old notion that syphilis of the nervous system is caused by a late invasion and realize that the spirochetes gain access to the meninges and the cerebrospinal fluid early in the infection, causing at this time the various manifestations which have been in the past two or three years so carefully studied under the name of neuro-recurrences. A proper grasp of what is taking place at this time, with a knowledge of the means of combating it, will limit the number of hopeless invalids who are now filling our institutions and increasing the burden of our tax-payers. The older treatment by mercury alone or combined with potassium iodid failed to sterilize the infection, except in a minority of cases. This statement needs no proof, as the large number of cases of nerve syphilis are striking witnesses of the fact. Attempts by intensive mercurial treatment to prevent or cure some of the forms of nerve syphilis so signally failed, that we took refuge in the belief that we were dealing, not with the direct results of syphilis, but with degenerative processes that were only indirectly due to it. The discovery by Noguchi and Moore of spirochetes in the central nervous system in paresis and tabes has definitely corrected this erroneous conception, so that

now we know we are dealing with syphilis and not with para-syphilis. We must therefore endeavor to adapt our treatment of these forms of the disease when established in conformity with the treatment of other infections of the cerebrospinal axis. Following the method of Flexner in cerebrospinal meningitis, Swift and Ellis, by the direct intraspinal treatment, have accomplished results which were not possible by the intravenous use of the drug. In well-established cases of tabes and paresis we may hope, under the best conditions, to check the further progress of the disease, cure certain individuals and relieve others of many distressing symptoms. Experience with the intraspinal treatment has been such as to encourage its more extended use in cases which do not yield to intravenous medication alone.

We will do more for the future security of our patients by so directing our treatment in the early months of the infection as to insure them against the development of these serious forms of nerve syphilis, and this can doubtless be done by intensive treatment, so controlled by the Wassermann reaction and by lumbar puncture, until the cerebrospinal fluid becomes normal and remains so. From failure on the part of the patient to cooperate and from skepticism or ignorance on the part of the medical man, the ideal result outlined will require years to accomplish, but that it can and will be accomplished in many cases is the firm belief of the writer. More uniformity in teaching and more systematic instruction of students in syphilography should be the aim of our medical schools, so that our future physicians shall realize the serious nature of the infection and the means of combating it.

The development of a well-defined plan of treatment has been a process of gradual evolution and is by no means as yet perfect. We have, however, been able to separate the symptoms produced by the drug from those caused by the infection. For example, the so-called nerve recurrences no longer occur in cases systematically treated with salvarsan alone or combined with mercury, so that it can be affirmed in a positive manner that they were the result of imperfect methods of employment and incomplete sterilization.

In order to avoid the toxic effect of salvarsan, it should be given in small initial doses, until the tolerance of the patient is determined, and then the dose may be gradually increased. In early syphilis and in syphilis of the nervous system a few doses of mercury intramuscularly should precede the systematic use of salvarsan. The best results are obtained by giving it in series of from four to six injections, at intervals of about ten days, combining it with intramuscular injections of mercury salicylate at weekly intervals and following the salvarsan series by eight or ten intramuscular injections of mercury. At the end of this course of treatment, a month's interval should elapse and the series of salvarsan and mercury injections repeated. Two or more such courses of treatment may be required in early syphilis before the Wassermann reaction is influenced. In late syphilis and in hereditary forms of the disease many such series may fail to change the reaction.

In the late manifestations of syphilis it is important also not to forget the remarkable effects of the iodid of potassium in combination with mercury. We have no more potent remedy in the pharmacopoeia than the iodids in resolving gummata, relieving the pains of periostitis, and rendering patent the blood-vessels occluded by syphilitic infiltration of their walls. In the interest excited by new drugs the benefits of the older ones are not to be forgotten.

Experience has enabled us to state that the disease is only certainly serologically curable in its early stages, and if we do not succeed in permanently changing the reaction at this time, we can not be certain of changing it by the most intensive and prolonged treatment. This statement should not be taken to mean that only early syphilis is curable, but that the result from treatment in old infections is less certain serologically than in earlier ones. Whether a persistent positive Wassermann reaction, after prolonged treatment, means potential syphilis or not, has not yet been answered.

To avoid the toxic action of the drug, some of the best syphilographers are advocating small or medium sized doses of 0.3 to 0.4 gm. for men and 0.25 to 0.35 gm.

for women. These doses can be repeated at shorter intervals and kept up for a longer time than the maximum doses at first advocated. The results from a continuous action of the drug over a long period are more certain therapeutically and attended with less danger than a few massive doses at longer intervals. It is possible in early syphilis, by the treatment outlined, to sterilize the patient and to obtain a permanent change in the Wassermann reaction in from four to six months. Such results have been confirmed by the writer in patients who have been under observation for from two to three years. Reinfections have been observed in two, and three others who have married have healthy children.

All powerful drugs have their unpleasant consequences and by-effects. Arsenic in the form of salvarsan and neosalvarsan is no exception to this rule. Some patients are unduly sensitive to it and manifest arsenic rashes, gastro-intestinal irritation, icterus, peripheral neuritis, haemorrhagic encephalitis, and death. Compared with the whole number of individuals treated and the lack of care exercised in the administration of the drug in many instances, the number of fatalities is surprisingly small when we consider that we are dealing with a remedy as powerful as this one. The length of this editorial will not permit any extended criticism of the causes which have led to a fatal issue in some of these cases, but it can be stated that a majority of them have resulted from imperfect technique and from ignoring the contra-indications to the use of it. With perfect technique in patients with sufficient kidneys, it is practically free from danger if the dosage is not too large and at too short intervals. The writer's experience has not led him to abandon the older methods of dilution for the concentrated solution. The amount of fluid employed is 180 c.c. in the case of old salvarsan. Of the latter, 0.6 gm. is dissolved in 80 c.c. of freshly distilled water, alkalized with 15 per cent. caustic soda solution and diluted with 0.5 per cent. saline to 180 c.c. For the neosalvarsan, the dilution is 0.9 gm. in 100 c.c. of cool distilled water. The drug is given slowly by the gravity method, so that from six to eight minutes are consumed

in one administration. No anaphylactic reactions have been seen in more than 8,000 administrations of the drug. By proper preparation of the patient and by subsequent rest of half an hour it appears to be entirely safe as an office or dispensary procedure, providing patients go home and to bed until the following day. In nerve syphilis, and in early florid syphilis the Herxheimer reaction may occur. This reactivation of recent or old foci is seen in secondary eruptions and in tabes it causes a temporary distressing aggravation of the pains and focal symptoms. Reactivation in tabes and paresis usually occurs after the first few injections and the improvement in such cases is correspondingly greater. In focal brain lesions, convulsions or paralysis may be temporary manifestations.

In the degenerative forms of tabes the effect of mercury may be deleterious, and in cases in which the interval between doses of salvarsan is too short we may get the cumulative effect of the arsenic. Because of the failure of mercury alone to influence tabes and paresis, and also from their effect in hastening degenerative changes, the combination of mercury with salvarsan in these affections should not be employed as a routine method but only in selected cases. The more active and recent the affection in the brain and cord, the greater the indications for their combined use. In old cases with degenerative effects in the foreground, there is less reason for the use of mercury. Persistent intravenous treatment with salvarsan in tabes and paresis and other forms of cerebrospinal syphilis, if without effect on the cells, Wassermann reaction or symptoms, should be followed by intraspinal injections.

In conclusion, it is possible with salvarsan alone, when properly administered in the early stages of the infection, to abort it. This has been demonstrated by the persistence of a negative Wassermann reaction over a period of more than two years and by cases of reinfection.

It has a much more rapid effect than mercury on the contagious lesions of the disease, limiting the time during which the patient is a menace to his surroundings. In

the later period of the infection, combined with mercury, it has a more marked influence over the clinical manifestations and the Wassermann reaction than mercury alone. In malignant syphilis there is no drug known which has such a marvelous influence on the symptoms. In cases which are resistant to mercury, or in which mercury has been administered over a long period of years with repeated relapses and persistence of a positive Wassermann reaction, salvarsan is the drug above all others to control the manifestations.

In syphilis of the nervous system which does not yield to the usual methods of treatment, intravenous injections of salvarsan, supplemented by the intraspinal administration, offers more to the patient than any therapeutic measure at our command.

Treatment of Syphilis. Until we know the cause of a disease its treatment must be empirical. Knowing the cause of a disease, we cannot gauge the effects of the treatment until a sufficient number of years has elapsed to enable us to do so from clinical experience, since no tests can be sufficiently relied upon to take the place of clinical experience.

McDonagh⁷ believes that the *Spirocheta pallida* is not the actual cause of syphilis. It is merely the adult male of a complicated life-cycle. There is also a female, and spores result from the fertilization of the female cell by the *Spirocheta pallida*. The adult sexual bodies are the main cause of the symptoms, while the spore is the cause of the disease. It must be remembered that the tendency of all protozoal diseases, the symptoms of which are dependent on the completion of a life-cycle by the organism causing infection, is toward spontaneous cure, as the longer the parasite is in the host the less able is it to complete its cycle, and the less influence treatment has upon it.

Although treatment may do much to prevent the organism from completing its life-cycle, the host does more and, one may say, in effect, that treatment is only able to prevent the parasite from completing its cycles pro-

(7) Brit. Med. Jour., October 10, 1914.

vided it is prescribed sufficiently early in the onset of the infection. Salvarsan will kill the spores in the earliest stages of the disease, while it is without effect in the late stages. In the late stages the symptoms vanish, not from destruction of the spores, but from the destruction of the ripe gametes to which the spores give rise. Therefore it is necessary to diagnose a recent infection as soon as possible, and without delay to give treatment which will be sufficient to cure the case. Excision of the primary sore, when possible, is essential, and a clinical observation in support of this view is the fact that many primary sores which become phagadenic are not followed by further evidences of syphilis, or, in those which are followed by symptoms, their onset is frequently delayed for months.

Salvarsan is the most potent antisyphilitic drug we at present possess; neosalvarsan is considerably feebler in its action. The majority of the patients with primary syphilis to whom one injection of salvarsan was given over four years ago are now both clinically and serologically sound.

The majority of the patients with primary syphilis to whom two injections of neosalvarsan were given when the drug first came on the market—that is, three and one-half years ago—have developed symptoms since. Of those who were already in the stage of general infection, nearly all showed recurrence within a year, and many within three months.

It is only since the rule has been followed of giving as many injections as are necessary to procure a negative Wassermann reaction in the blood taken between the seventeenth and forty-eighth hour after the last injection, and to prescribe a year's treatment with mercury, that the fewest recurrences have been observed. Probably, in a few more years, in many of those cases which have not so far recurred the patients will develop symptoms, but, until our knowledge increases, this procedure appears to be the best.

In the primary stage, a cure is possible if sufficient injections of salvarsan are given to procure a negative

Wassermann reaction in the blood withdrawn within the limits specified, and the treatment is further augmented by twenty-four intramuscular injections of mercury, given in three courses of eight weeks, within the twelve months. In the secondary stage a cure may possibly be obtained, and it is wise to continue the mercury for another year.

Success for the same treatment in the latent stage of the disease and in the stage of early recurrence is improbable, while in the stage of late recurrences, gummata, and nervous syphilis a cure is impossible—that is, broadly speaking, since spontaneous cures may occur in any stage.

In the primary stage from three to five injections, and in the secondary stage from six to nine injections, are required. It is best to give the five and nine injections respectively, as the Wassermann reaction is apt to be contradictory. In late cases, even fifteen or more injections of salvarsan may fail to procure a negative Wassermann reaction, and supposing a negative Wassermann reaction be obtained, it is not long before it becomes positive again.

In late cases, it appears wiser to give two or three injections of salvarsan to heal the symptoms, and to augment it with a course or two of mercury and iodids, meanwhile informing the patient that he should place himself under treatment again the moment the symptoms reappear. Such a patient may go for years without a recurrence and, should symptoms reappear, they will probably do so in the site of the previous recurrence.

It is universally agreed that the best way to give salvarsan is intravenously, and the requisite number of injections should follow upon one another at intervals of not longer than seven days.

A most important point to remember in salvarsan treatment is that, if too few injections are given to a patient with infectious symptoms, should the symptoms recur they will simulate those for which the drug was prescribed. After insufficient salvarsan treatment, symptoms recur before the mercury which has been pre-

scribed afterwards, usually in the form of pills, has had time to exert its action. Insufficient salvarsan treatment in the early stages of syphilis will do more harm than good, as it gives the patient a false sense of security, and renders him for a longer period a danger to the community.

Owing to the spasmodic and insufficient manner in which salvarsan is prescribed, tabes and general paralysis of the insane will in a few years' time increase even more rapidly than is the case to-day. To pregnant women who are syphilitic McDonagh gives, as soon after they have conceived as possible, six intravenous injections of neosalvarsan, and continues the treatment with mercury till as near the time the child is to be born as possible.

Abortive Treatment of Syphilis With Salvarsan and Mercury. Hecht⁸ gives his method as follows:

1. The earlier the treatment is begun, the greater the possibility of aborting the disease.
2. The most favorable cases are those without adenopathy, with a negative Wassermann reaction, and a good localization, permitting of complete excision.
3. The treatment consists in from one to three intravenous injections of salvarsan (0.4 to 0.6 grs.) and from eight to twelve calomel injections (0.5 c.c. of a 10 per cent. emulsion).
4. When possible, the chancre should be widely excised and the scar covered with gray plaster or mercurial ointment until after healing.
5. With a positive Wassermann reaction, more is to be expected from mercury than from salvarsan.
6. After cessation of treatment, a physical and serum examination should be made every two months.
7. Reappearance of a positive Wassermann reaction is an indication for further treatment.
8. If after eight months' treatment the Wassermann reaction is still negative, the chances for a cure are good.
9. It is impossible to say at present when an individual is cured. A provocative Wassermann test should always be made.

(8) Arch. Derm. Syph., May, 1914.

Intradural Injections of Neosalvarsan in Syphilis of the Nervous System. The solution used by U. J. Wile⁹

(9) Jour. Amer. Med. Ass'n., July 11, 1914.

for injection consists of a 6 per cent. solution of neosalvarsan in distilled water. This solution is hypertonic and made of such a concentration that each minim must contain 3 mg. of the drug. The dosage injected is from 3 to 12 mg.—that is, from 1 to 4 drops of the solution, which is made up as follows:

An ampule containing 0.3 gm. of neosalvarsan is dissolved in 5 c.c. of freshly distilled water. If the ampule contains 0.6 gm., 10 c.c. of water are used. In both solutions, each drop will contain 3 mg. of the drug. The syringe employed for the injection is accurately graduated in drops. The patient is placed in a position for lumbar puncture, either sitting or lying, according to the choice of the operator. The puncture is then made with a needle, the end of which fits the graduated syringe. After a few drops of the spinal fluid have flowed out of the cannula, or a greater quantity if a diagnostic puncture is desired at this time, the syringe is fitted into the needle, and the fluid is allowed to run back into the syringe barrel, thus mixing with the amount of the drug in the barrel. The mixed spinal fluid and drug are then gently forced into the canal, and slight suction is made on the syringe to withdraw a second amount of fluid, which washes out the needle. This is then reintroduced, the needle is quickly withdrawn, and the patient placed in the Trendelenburg position, in which position he is allowed to remain for at least an hour.

In all, twenty-five injections were given to fifteen different patients. The classification of the cases treated is as follows: tabes dorsalis, seven; general paresis, three; cerebrospinal syphilis, three; tabo-paresis, two.

Of the fifteen patients thus treated, two are dead; seven are markedly improved, both subjectively and in the objective findings in the cerebrospinal fluid; three patients having general paresis were given only a single injection and showed no improvement, nor were they made any worse by the treatment; one patient showed

an improvement after a single injection with a relapse of symptoms, and no subsequent treatment was given; and one patient was markedly improved with respect to the oculomotor palsy, but showed progression of the spinal feature of the disease in a progressive paraplegia.

The patients who have thus far been treated are too few to permit the drawing of any but tentative conclusions. In general, patients with cerebrospinal syphilis other than tabes or paresis did decidedly better than those in whom either one or both of those two conditions were present. It is noteworthy that in those individuals with tabes in whom no bladder or rectal symptoms were present did especially well. It would seem, therefore, that such symptoms constitute contra-indications for the treatment as it is given at present.

The marked improvement in the objective findings in the spinal fluid following treatment, in practically all forms of syphilis thus treated, even in the absence of subjective improvement, lead one to hope that this form of treatment is along the right line for checking, or, indeed, in some cases even curing, central nervous involvement.

Individuals to be thus treated should be carefully selected. For the present, at least, this form of treatment should be restricted to cases in which other forms of treatment have proved inefficient.

In all cases, the danger of the treatment in its present unperfected state should be pointed out to the patient and his family, and the responsibility for its administration should be shared by them. It is to be hoped and expected that more careful study and selection of cases will prove the intradural injection of neosalvarsan a potent remedy in combating cases of cerebrospinal syphilis.

Dangers of Salvarsan Disappear After the First Injections. Even if we admit that physicians are less inclined now than formerly to report the accidents following salvarsan and neosalvarsan, there can be no doubt that the accidents are rapidly diminishing, notwithstanding the fact that the yearly number of injec-

Intradural Injections of Neosalvarsan in Syphilis of the Nervous System. The solution used by U. J. Wile⁹

(9) Jour. Amer. Med. Ass'n., July 11, 1914.
for injection consists of a 6 per cent. solution of neosalvarsan in distilled water. This solution is hypertonic and made of such a concentration that each minim must contain 3 mg. of the drug. The dosage injected is from 3 to 12 mg.—that is, from 1 to 4 drops of the solution, which is made up as follows:

An ampule containing 0.3 gm. of neosalvarsan is dissolved in 5 c.c. of freshly distilled water. If the ampule contains 0.6 gm., 10 c.c. of water are used. In both solutions, each drop will contain 3 mg. of the drug. The syringe employed for the injection is accurately graduated in drops. The patient is placed in a position for lumbar puncture, either sitting or lying, according to the choice of the operator. The puncture is then made with a needle, the end of which fits the graduated syringe. After a few drops of the spinal fluid have flowed out of the cannula, or a greater quantity if a diagnostic puncture is desired at this time, the syringe is fitted into the needle, and the fluid is allowed to run back into the syringe barrel, thus mixing with the amount of the drug in the barrel. The mixed spinal fluid and drug are then gently forced into the canal, and slight suction is made on the syringe to withdraw a second amount of fluid, which washes out the needle. This is then reintroduced, the needle is quickly withdrawn, and the patient placed in the Trendelenburg position, in which position he is allowed to remain for at least an hour.

In all, twenty-five injections were given to fifteen different patients. The classification of the cases treated is as follows: tabes dorsalis, seven; general paresis, three; cerebrospinal syphilis, three; tabo-paresis, two.

Of the fifteen patients thus treated, two are dead; seven are markedly improved, both subjectively and in the objective findings in the cerebrospinal fluid; three patients having general paresis were given only a single injection and showed no improvement, nor were they made any worse by the treatment; one patient showed

an improvement after a single injection with a relapse of symptoms, and no subsequent treatment was given; and one patient was markedly improved with respect to the oculomotor palsy, but showed progression of the spinal feature of the disease in a progressive paraplegia.

The patients who have thus far been treated are too few to permit the drawing of any but tentative conclusions. In general, patients with cerebrospinal syphilis other than tabes or paresis did decidedly better than those in whom either one or both of those two conditions were present. It is noteworthy that in those individuals with tabes in whom no bladder or rectal symptoms were present did especially well. It would seem, therefore, that such symptoms constitute contra-indications for the treatment as it is given at present.

The marked improvement in the objective findings in the spinal fluid following treatment, in practically all forms of syphilis thus treated, even in the absence of subjective improvement, lead one to hope that this form of treatment is along the right line for checking, or, indeed, in some cases even curing, central nervous involvement.

Individuals to be thus treated should be carefully selected. For the present, at least, this form of treatment should be restricted to cases in which other forms of treatment have proved inefficient.

In all cases, the danger of the treatment in its present unperfected state should be pointed out to the patient and his family, and the responsibility for its administration should be shared by them. It is to be hoped and expected that more careful study and selection of cases will prove the intradural injection of neosalvarsan a potent remedy in combating cases of cerebrospinal syphilis.

Dangers of Salvarsan Disappear After the First Injections. Even if we admit that physicians are less inclined now than formerly to report the accidents following salvarsan and neosalvarsan, there can be no doubt that the accidents are rapidly diminishing, notwithstanding the fact that the yearly number of injec-

tions has reached the two million mark. According to Leredde,¹ the number of deaths has been as follows:

(1) Bull. Soc. fran. de Dermat. et de Syph., 1914, p. 91.

16	deaths in	1910
92	" "	1911
66	" "	1912
37	" "	1913

The number of injections, however, has increased as follows:

50,000	injections	in	1910
800,000	"	"	1911
1,280,000	"	"	1912
2,000,000	"	"	1913

If the deaths were due to the toxic action of the drug, they should increase *pari passu*. Arranged according to the number of injections received by the patient, the table shows that of 211 cases

104	occurred	after	the	1st	injection
55	"	"	"	2nd	"
13	"	"	"	3rd	"
8	"	"	"	4th	"
1	"	"	"	5th	"
1	"	"	"	6th	"
1	"	"	"	7th	"

There are but two interpretations of these figures:

1. The fatalities are not due to intoxication.
2. Except in moribund cases, or in intercurrent infections, the fatalities are due to: (a) errors of technique; (b) disregard of contra-indications; (c) reaction of Herxheimer.

The first should be eradicated; the second should be respected; and the third should be anticipated.

One of the common faults of technique is allowing the solution to oxidize by standing exposed to the air. In one death the solution was five days old and in another fifteen days. Another fault is too short an interval between injections.

The decrease in the deaths after the first injection, without a comparable decrease after the second injection,

tion, is due to the fact that the Herxheimer reaction occurs most frequently at that time. They follow in tabular form:

16	occurred	after	the	1st	injection
30	"	"	"	2nd	"
9	"	"	"	3rd	"
1	"	"	"	4th	"
1	"	"	"	5th	"
1	"	"	"	6th	"

These deaths continue, because, although the physicians have corrected their faulty technique and the deaths after the first injection have decreased, nevertheless they have disregarded the possibility of a Herxheimer fatality.

The Fate of Salvarsan and Neosalvarsan in the Body.

At the suggestion of Ehrlich, Stühmer² undertook to investigate what becomes of the two drugs when injected intravenously. Rabbits were used for the experiment. Various sized doses in different concentration were injected, after which the amount of the drug in the blood and viscera was determined at regular intervals.

It was found that of the three preparations, namely, acid and alkaline salvarsan, and neosalvarsan, the latter was distributed most uniformly throughout the body, even in a concentration of 1:1. The alkaline salvarsan, in the usual dilutions, differed but slightly in this respect, whereas the acid salvarsan seemed to have an especial affinity for the lungs, which appeared to filter the drug from the blood. In concentrated solution (1-25), the alkaline salvarsan had a similar affinity.

A very short time after the injection, all the preparations in great part disappear from the body. The lungs, liver and spleen retain the largest amount. These organs thus form a depot, from which the blood constantly absorbs the deposit of the drug, and it is in this manner that the clinical effect is produced. The alkaline and acid salvarsan remain as long as three days, whereas the neosalvarsan disappears within twenty-four hours. Salvarsan in great part passes unchanged through

(2) Arch. Derm. Syph., 1914, p. 538.

the kidneys but is excreted through the bowel. Such a large amount is thrown into the intestine, that should there be a disturbance of function, oxidation products may form which, when reabsorbed, may lead to severe intoxication. With repeated injections, the absorption and storage capacity of the various organs are increased.

The Fate of Intramuscular and Subcutaneous Injections of Salvarsan. Takahashi³ found experimentally that about the deposit of salvarsan there develops in the course of fourteen days a widespread necrosis, with acute inflammatory reaction. The whole mass becomes walled-off by leukocytes. About the necrotic area granulation tissue forms and eventually invades the mass, which becomes absorbed. The regeneration occupies about 350 days and is followed by scar-tissue. Three stages of the process can be made out. In the first stage, that of the tissue necrosis, the soluble salvarsan and the fine particles are carried to the lymph-vessels. Most of it is eventually excreted by the kidney, and only a small amount remains in the body. In the second stage, that of the formation of the granulation tissue, the salvarsan which becomes transformed into definitely soluble granules is but very slightly absorbed. With abscess-formation, most of it is evacuated with the pus.

In the third stage, the remaining granules are taken up by the cells of the granulation tissue, chiefly the giant-cells. The time required for the total process is about 400 days.

The central nervous system apparently absorbed none of the preparations, except that neosalvarsan appeared to have an affinity for the membranes. Hence, for meningeal or cerebral lesions it would appear that the best effect should be obtained from neosalvarsan, traces of which were found in the cerebrospinal fluid, probably by absorption from the meninges.

Intravenous Administration of Mercury in Syphilis. The history and literature are reviewed by J. Kingsbury and P. E. Bechet,⁴ who also describe the technique which they follow.

(3) Arch. Dermat., 1914, p. 340.

(4) Trans. Sec. Derm. A. M. A., 1914.

This method was first used by Bacelli in 1893, and subsequently by Blaschko, Lewin, Chopping, Lane, Abadie, Campana, and Stoukowskoff and others. The method in recent years has apparently fallen into disuse, inasmuch as very few articles on the subject are found in the literature. This may be due to the rather discouraging attitude of Fournier, who looked on the method with disfavor. He is under the impression that a toxic agent, such as mercury, suddenly placed in contact with the endometrium, may possibly exert a deleterious effect on it. His supposition is based on the experiments of Ullman. While Ullman has never seen an animal die after the intravenous injection of large doses of mercury, yet in a few cases in which death occurred later there were no lesions which would account for the death of the animal, and Fournier reasons that death might have been caused by paralysis of the heart, engendered by the previous injections of mercury. Two comparatively recent articles on the intravenous injection of mercury in the treatment of syphilis are by Meyer, whose results were disappointing, and Lydston, whose results in eight cases were very gratifying. Wernigk appears enthusiastic, after twelve years of experience with the intravenous injection of mercury. Balzer, at the French Medical Congress of 1904, endorsed it for cerebral and ocular syphilis. Ravaut uses the cyanid of mercury, intravenously, as a preliminary to salvarsan therapy.

Kingsbury and Bechet have used the method in a large number of cases of cutaneous syphilis. They first used the bichlorid in doses of from $\frac{1}{4}$ to $\frac{1}{2}$ grain in distilled water. On an average, six injections were given in each case. The best results were attained with this salt, but they also used the benzoate in a 1 per cent. solution in normal saline, of which the dose was from 2 to 12 c.c. While the results with this salt were good, they were inferior to those obtained with the bichlorid.

The technique of the injection is simple, provided that the patient has prominent veins; otherwise, the percentage of failure to get the needle in the lumen of the vein is in proportion to the experience of the operator in intra-

venous work. The amount of solution used varies, of course, with the particular dose it is desired to give, but it rarely exceeds 12 c.c.

The advantages of the intravenous method are: immediate introduction of the curative agent in the circulating blood, rapid therapeutic results, mathematical dosage, and absence of pain. The most important disadvantage is the occasional occurrence of phlebitis, and periphlebitis, which seemed more frequent after the use of the bichlorid than of the benzoate; this complication, however, occurred only in the early cases, when the solution used was more concentrated. A small number of the patients suffered from ptyalism, and a few others developed mercurial diarrhea, but in none of the cases did these complications cause anything more than a temporary disturbance.

The results in the author's hands, where the rapid removal of lesions was desired, were uniformly good. They were impressed with the prompt therapeutic results obtained with this method, and are strongly convinced that despite its obvious disadvantages it is of great value in selected cases. It is not to be used indiscriminately, however, and they do not recommend it for routine administration.

Facial Paralysis Following Treatment With Arsenobenzol. Since salvarsan has come into general use in the treatment of syphilis, involvement of the nervous system, principally paralysis of the cranial nerves, has been more frequently observed, perhaps, than in the days of the mercurials. These accidents have been largely attributed to the toxic action of salvarsan. But a more careful study has shown that the nerve lesions were due to insufficient treatment. Sicord, in 1912, divided these cases into three groups: (1) a toxic action of the drug upon the nerve, chiefly the acoustic, due to the affinity of arsenic for the nerve; (2) meningeal symptoms, probably due to the Herxheimer reaction; and (3) the *neuro-récidive*, appearing a number of weeks after the last injection, due to incomplete sterilization, and subsiding with further treatment.

The following case reported by Demanche⁵ is a good illustration of the last group. A young woman was treated in January, 1914, for secondary manifestations of syphilis. Four intravenous injections were given, representing in all 1.7 gm. of salvarsan. In March, the Bauer reaction was still slightly positive. In April, she developed a peripheral paralysis of the superior and inferior branches of the left facial nerve. The cerebrospinal fluid showed an abnormal cell-count of 195 and a positive Wassermann reaction. Another injection of 0.5 gm. of salvarsan caused a disappearance of the symptoms within ten days. Two weeks after the injection the count had dropped to 34 and the fluid was almost negative to the Wassermann test.

The Herxheimer Reaction. Many years have elapsed since Herxheimer described the reaction which now bears his name, and during this time many erroneous notions concerning it have arisen. Milian⁶ gives a general review of the opinions regarding the reaction, together with a differentiation between the reaction of Herxheimer and that of intolerance. By the former is understood the inflammatory reactions which occur in syphilitic tissues as a result of specific treatment. The reaction has been more frequently observed since the advent of arsenical medication, but did occur with the mercurials. All the skin, mucous membranes, and visceral lesions may react, but the macular exanthems are the ones most commonly observed (90 per cent.).

When the reaction occurs, the skin or the mucous membrane at the site of the lesion becomes turgescient and may weep, particularly if it be an infiltrated lesion. The roseola, however, gives the most typical reaction. Following the injection of salvarsan an exanthem may appear within two hours, usually at the time of onset of the febrile reaction; or an erythema of a multiform type may occur. As a rule, however, a simple roseola appears shortly following the injection, and disappears within six hours. Along with these induced roseolas, one usually sees an exaggeration of the pre-existing eruption, of

(5) Bull. Soc. franc. de Derm. et de Syph., 1914, p. 265.

(6) Ibid, 1914, p. 265.

which the elemental lesions become larger and redder, and occasionally even edematous.

The papular syphilids, even those which were scarcely noticeable before, stand out and become red and succulent. Likewise, the pigmented syphilids and the malignant precocious syphilis may show marked changes.

The mucous membrane lesions react less frequently than the cutaneous lesions, but the process is similar when it does take place.

The gummata may also show the reaction. When not open, they become swollen and turgid. When ulcerated, they enlarge and emit an abundant serous discharge.

Among the general and visceral symptoms which take place after the first injection, fever is the most common and the most important. It is frequently difficult to say whether the manifestations are those of a Herxheimer reaction or of an intolerance for the drug. As an aid in differentiating the two, Milian mentions the following points:

In the reaction of Herxheimer; (1) the symptoms decrease in intensity with each injection of the same dose or with even larger doses; (2) they diminish *pari passu* with the decrease in the syphilitic manifestations; (3) so long as this reaction continues, the Wassermann reaction remains stationary, or even increases in intensity; (4) the cerebrospinal fluid contains cells which may be augmented in number with each injection.

The reactions of intolerance, however, take practically the opposite course.

1. The general and febrile reaction increases or remains the same with each injection, regardless of the size of the dose.

2. The reaction continues in spite of amelioration, or even the disappearance, of the syphilitic symptoms.

3. The reaction persists, although the Wassermann reaction may decrease in intensity or become negative.

4. The reaction may continue to occur with a completely negative cerebrospinal fluid.

Among the visceral reactions, the most important are those occurring in the liver. In syphilitic diffuse hepatitis, there is an exacerbation of the icterus, which may

progress from a greenish-yellow to a deep greenish-black. This exacerbation is not to be confused with the toxic icterus of intolerance.

The Herxheimer reaction of the central nervous system affects either the meninges or the cranial nerves. The deaths from salvarsan are practically all due to a serous encephalitis, and are not to be explained by the Herxheimer reaction, because most of them have occurred in the absence of syphilis. The symptoms preceding death usually appear about the third day after the injection as a severe headache, followed by convulsions, coma, and death within twenty-four hours.

The reaction of Herxheimer is frequently found of much value in indicating a latent syphilis; and is an indication for further treatment.

The Nitritoid Crisis and the Serous Apoplexy of Salvarsan. Milian⁷ believes that the severe reactions sometimes following salvarsan injections are not toxic but mechanical, and due to a vaso-dilatation chiefly of the chorioid plexus, causing nausea, vomiting, and other familiar unpleasant symptoms. If the patient at the time of the injection says he smells ether, it indicates a hypersensitiveness to the drug and a coming crisis. As a prophylaxis an immediate hypodermic injection of adrenalin should be given and repeated if necessary. This he has found to be effective in warding off an attack.

[In the course of an experience with a great many injections, it has been observed that fully 75 per cent. of all patients will describe an odor of ether if asked if they smell anything. The usual supposition of the patient is that the odor is that of the salvarsan. There appears to be no relation existing between the detection of the odor and a subsequent reaction.—Ed.]

GENITO-URINARY SURGERY.

Operative Treatment of Genital Tuberculosis. The term "genito-urinary tuberculosis" should be abandoned, state Cabot and Barney,¹ and we should come to

(7) Bull. Soc. de derm. et de syph., 1914, p. 104.

(1) Jour. Amer. Med. Ass'n., 1913, Vol. 61, p. 2056.